

An Epidemiologic Health Study of Manganese Exposure in adult residents of
East Liverpool, Ohio

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1. STUDY AIM, BACKGROUND AND DESIGN

The proposed study aims to answer the following questions:

- Is external Mn exposure (Mn-air) associated with biomarkers of internal Mn dose [Mn in blood (Mn-B), toenails (Mn-T), hair (Mn-H)] and neuropsychological and neurological function in adults?
- Does the neuropsychological function of a group of Mn-exposed adults differ significantly between groups with different levels of exposure to Mn-air?

Exposure Background:

On November 16, 2010 the U.S. Department of Health and Human Services, Agency for Toxic Substances and Disease Registry (ATSDR) presented residents of the town of East Liverpool, adjacent to the Ohio River, with an air quality report describing the potential health risks from ambient metals. Analyses of the U.S. EPA's air monitoring data at three locations in East Liverpool have shown elevated ambient air levels of manganese (Mn) and chromium-III (Cr^{III}) over a period of nine years and eight months (between January 1999 and September 2009). Mn-air levels in East Liverpool (Water plant monitor) were found to be on average about 10 times higher than those in another Mn-exposed Ohio town (Marietta), which, along with a similar non-industrially Mn-exposed town (Mt. Vernon), has been examined recently in a health study conducted by the P.I. and her colleagues. Ohio EPA identified the S.H. Bell Company, a facility that warehouses and packages primarily raw metals (including Mn) from all over the world, as an exposure source contributing to these elevated levels. The present study seeks a) to determine the possible health risks to residents of the high Mn-exposure in East Liverpool, and b) to compare any health effects between the towns (exposed and comparison) currently being studied by this team of investigators.

There is a time urgency to perform a health study of the Mn health risks in East Liverpool because the S.H. Bell Company has been required by Ohio EPA to reduce the community's exposure to Mn emissions. In two Ohio EPA and US EPA enforcement actions, the plant was asked to comply with the following guidelines in order to remain in operation: pave a dirt road on the State Line property, install a dust suppression program, enclose some storage piles, improve dust collection, and tarp all trucks leaving the S.H. Bell facility. The site upgrades were completed in 2008 and it is anticipated that Mn-air will have decreased by the middle of 2011. Ohio EPA also plans to continue the air monitoring and, moreover, have already installed

a PM₁₀ monitor and plan to install a PM_{2.5} monitor which will assess the respirable fraction of the Mn particles.

The experienced research team proposing this health evaluation is prepared to conduct such a study of East Liverpool residents on short notice because they have already developed epidemiologic methods and applied them in the current health study being completed of the Mn-exposed town of Marietta, Ohio and the unexposed comparison town of Mt. Vernon, Ohio. Relevant health questionnaires - including questions on demographic and residential history, symptoms and illnesses, environmental characteristics, such as intake of Mn and iron in diet, time spent indoors and outdoors - have already been developed and tested and are appropriate for use in East Liverpool with minimal changes. Ohio Department of Health has pledged to assist the P.I. and study investigators with news media co-ordination and lending state-level support to the study team. Additionally, Dr. Michelle Colledge, who authored the East Liverpool Air Quality Report of November 16, 2010, will collaborate on the analyses of the air Mn exposure (ATSDR, 2010). Advanced staff members from the ATSDR and the U.S. and Region 5 EPA will collaborate with the team of investigators, trained neuropsychological testers, medical experts, and statisticians who have been working conjointly on the Marietta-Mt. Vernon study. They will be available this calendar year (2011) and are willing to work on the proposed on-site applied health research study in East Liverpool. The proposed study offers the opportunity to examine an additional, more highly Mn-exposed community, and to compare the results to the two towns in Ohio under current study.

Exposure source:

Ambient air monitoring has already been conducted at three monitor locations near the S.H. Bell Company in East Liverpool and ambient Mn-air measurements are available from the Ohio EPA and the ATSDR for a period of nine years and eight months.

As described in the East Liverpool Air Quality Report by the ATSDR of November 16, 2010 (ATSDR, 2010), the S.H. Bell Company handles a great volume of raw and processed metal products. S.H. Bell has two locations in East Liverpool, approximately one mile apart: the Little England facility and the State Line facility. Ferrous and nonferrous materials are stored, transferred, and warehoused at both locations. The S.H. Bell Company is equipped to process, dry, crush, screen, and package their ore/materials for industry. Shipping occurs through river barge, truck, and rail. On most days, this includes shipping out 1.5 barges and 100-120 trucks (ATSDR Health Consultation report, 2010). Although the company employed 52 persons in 2007, by 2009, this number decreased to 26 workers. The results of air monitoring reported in the November 2010 East Liverpool Air Quality Report showed highly elevated Mn levels in air (ATSDR, 2010). Only two metals, Mn and Cr were identified as elevated in the air sampled over nine years and eight months. More specifically, all of the identified chromium particulate matter was Cr(III) – no Cr(VI) was noted. Cr(III) is not associated with an increased cancer risk and is not considered to be a health concern (ATSDR, 2010). The EPA's computation of a hazard quotient (HQ: ambient concentration divided by the reference concentration of 0.05 µg/m³) of 30 indicated the residences near the Water Plant air monitor (S.H. Bell State Line facility) have the highest non-cancer risk, with 99% of the risk "attributed to Mn" (ATSDR, 2010).

The monitors located near the two S.H. Bell facilities in East Liverpool are (See Appendix A of

this report and the Air Quality Report of November 16, 2010):

- 1. Water Plant** monitor immediately adjacent to the S.H. Bell State Line facility. The air monitor is located approximately 250 feet W from the State Line facility with average Mn TSP concentration of $1.30 \mu\text{g}/\text{m}^3$, range $0.10-23.0 \mu\text{g}/\text{m}^3$
- 2. Maryland Avenue** monitor located about 0.30 miles to the north-northwest of the S.H. Bell Little England facility – with average Mn TSP concentration of $0.18 \mu\text{g}/\text{m}^3$, range $0.01-1.0 \mu\text{g}/\text{m}^3$
- 3. Port Authority** monitor located approximately 0.33 miles to the west-southwest of the S.H. Bell Little England facility with average Mn TSP concentrations of $0.26 \mu\text{g}/\text{m}^3$, range $0.02-1.9 \mu\text{g}/\text{m}^3$

Because the Water Plant monitor clearly shows the highest levels of Mn in air, the area around the water plant in a 2.5 mile radius will be the area studied under the proposed protocol. Additionally, census data indicates that this area has a sufficient number of housing units from which to recruit a random sample of 100.

The EPA has indicated that average Mn concentrations are between 0.04 and $0.05 \mu\text{g}/\text{m}^3$ in urban areas. The ATSDR also reports average levels in urban areas of $0.05 \mu\text{g}/\text{m}^3$ and the WHO reports concentrations near industrial Mn sites to be 0.2 to $0.3 \mu\text{g}/\text{m}^3$. The area around the East Liverpool air monitors is densely populated, making it an ideal natural laboratory to study the health effects of moderately high levels of Mn in air in an environmental setting.

Human Exposure to Manganese:

Manganese is a naturally occurring essential element and low levels of Mn in water, food, and air are ubiquitous. Although Mn is also contained in food, it is thought to be more readily absorbed from water and air. In certain geographic regions, long contact between groundwater and Mn in bedrock can lead to high levels of Mn in water (U.S.EPA, 2004). Industrial plants involved in the refining and processing of Mn ore have higher Mn emissions, which may affect the health of humans residing in close proximity. The Mn exposure route of most concern in the present study is inhalation. Blood biomarkers will reflect all routes of Mn exposure. Diet will be surveyed with a suitable brief diet questionnaire to assess approximate intake of Mn rich foods such as nuts, beans and tea and whole grains (rice, wheat, oats, etc.), but Mn in diet is not considered to have a contribution to adverse health effects. The proposed study will also provide pilot data that will subsequently help conducting an even larger, more comprehensive study by ATSDR at a later date.

In the occupational health literature there are many reports of workers exposed to Mn with adverse health effects. Miners, steel and alloy smelters, chemical plant workers over-exposed to Mn, and iron/steel welders are known to be at risk for developing a pattern of signs and symptoms showing a decline in psychiatric health (i.e. mood disturbance), deterioration of cognitive ability (i.e. problems with attention, memory, and information processing), and a

movement disorder similar to Parkinson's disease (PD) (i.e. a disturbance of gait, loss of balance, dystonia, bradykinesia, and tremor) (Bowler et al., 2007).

Environmental studies of airborne Mn have been relatively rare and results of a select few studies have been published. At the first major conference on the effects of long-term, low-level exposure to Mn in Little Rock, Arkansas in 1997, an inter-disciplinary international forum was held on state of the art research data on this issue, which was followed by publication of the peer-reviewed papers presented at that time. In this special April/June 1999 issue of the Journal of NeuroToxicology only 7 out of 33 published papers reported on environmental human exposure to Mn, including exposure to Methylcyclopentadienyl Manganese Tricarbonyl (MMT) (2 publications) and the neuropsychological effects of environmental Mn exposure (5 publications). Lynam et al. (1999) reported no effects of MMT and of ambient air levels of car emissions in Toronto, Canada. Zayed et al. (1999) also reported a lack of effects of potential exposure to MMT in residents near a gas station and underground parking garage, but did report "substantial concentrations of respirable manganese (Mn_R)".

Neuropsychological effects of environmental Mn exposure were reported by Mergler et al. (1999) in their study of 273 community residents in Quebec, Canada, for whom a relationship of lower neuropsychological function with higher Mn in blood was found. Higher levels of Mn were also shown to be associated with changes in coordinated upper limb movements and poorer learning and recall. An interaction between Mn and increasing age (>50) was found for motor tasks. Bowler et al. (1999) reviewed the literature on neuropsychiatric effects of Mn on mood and described these effects in the group of 273 community residents in Quebec. These effects were categorized to be anxiety, psychotic experiences, emotional disturbance, fatigue, compulsive behaviors and aggression and hostility. Baldwin et al. (1999) described the bioindicators and exposure data of the Mergler et al. (1999) study and reported that Mn in air samples of total suspended particulate measured at 4 sites, amounted between $0.009\text{ }\mu\text{g}/\text{m}^3$ and $0.035\text{ }\mu\text{g}/\text{m}^3$. These levels of Mn in air are considerably lower than those in East Liverpool.

Studies by Lucchini et al. (2007) report an increased prevalence of parkinsonian disorders associated with Mn exposure in the vicinities of ferroalloy industries in Northern Italy. Concentrations of Mn in settled dust measured in 206 municipalities were significantly higher near and downwind from two of four industrial plants. Near one of the four plants studied, airborne concentration of Mn in total dust averaged $300+533\text{ }\mu\text{g}/\text{m}^3$ (range 20-1600). The estimated range of ultrafine PM_{2.5} particles in six locations, within a distance of about 2 km from plant B (Lucchini et al., 2003) were also measured outside the plants in 2001 and showed a geometric mean of $0.69\text{ }\mu\text{g}/\text{m}^3$ (range 0.2-1.8). The respirable fraction of Mn was reported to be 25% to 90% of the total dust from the plants.

In 2007, Finkelstein and Jerrett (2007) re-visited the concerns over industrial Mn emissions and those due to combustion of gasoline MMT and investigated the association of PD and Mn exposure in 110,000 subjects from Toronto and Hamilton, Canada. They used residential postal codes and did geocoding to assign longitude and latitude coordinates for each resident. Thus, the residential locations were analyzed for distance from a major urban road. Hamilton residents were exposed to both mobile sources of Mn from MMT and industrial Mn emissions from steelmaking industry, while residents in Toronto were without "substantial"

industrial emissions of Mn. Manganese in total suspended particulate in Hamilton (TSP-Mn 50.5, to 92.1 ng/m³) was found to be significantly higher than in Toronto (9 ng/m³). Results of the prevalence curves for PD indicated that ambient exposure to Mn results in diagnoses of PD at an earlier age, which was postulated to be consistent with the theory that increased Mn exposure would be associated with increased neuronal loss in the aging process.

Although few comprehensive studies of environmental exposure to Mn have been reported, a small body of recent research has associated Mn exposure with learning and neuropsychological deficits in elementary school children. Wasserman et al. (2006) reported dose-effect relationship between concentration of Mn in drinking water and decreased IQ. Likewise, Chinese investigators reported that scores on tests of learning and neuropsychological functions were lower in elementary school children exposed to Mn in drinking water at levels of 241-346 ug/l than in children from a control group with very low Mn levels in drinking water. Levels of Mn in hair correlated with several neuropsychological scores. Additionally Zhang et al. (1995) reported lower levels of serum 5-hydroxytryptamine, dopamine, norepinephrine and acetylcholine esterase in the exposed children. Bouchard et al. (2007) reported a significant relation between levels of Mn in water and hair of children as well as an increase in indicators of hyperactive behaviors with Mn in hair.

In conclusion, although recent studies on children exposed to Mn- through drinking water show decrements in neuropsychological performance, none of the recent environmental studies on adults included a comprehensive neuropsychological test battery in the context of air measurements, such as those detailed in the East Liverpool air reports. Only the earlier work by Mergler et al. (1999) related Mn in air to neuropsychological function. This present study seeks to fill that gap and will utilize past knowledge gained from these studies by using a more refined and recently updated neuropsychological test battery, including the Computerized Adaptive Testing System (CATSYS) to assess hand tremor and body sway, in addition to geo-coded data in relation to the Mn air results already performed by ATSDR and EPA in East Liverpool, Ohio.

BACKGROUND

Air monitoring at the three locations near the S.H. Bell Company in East Liverpool has already been conducted by the Ohio EPA and the ATSDR over a period of over 9 years. This proposed project is to be conducted with a randomly selected sample of adult residents aged 30-75 years (under a contract between SFSU and the US EPA with partial in-kind contributions of personnel from the ATSDR and EPA). Randomly selected study participants will include 100 residents, selected from a purchased list of addresses in East Liverpool, OH, within a perimeter of 2.5 miles from the Water Plant air monitor. This study will include neurological and neuropsychological evaluations and measures of Mn exposure in air and levels of Mn in biomarkers measured in blood, hair, and toenails. Upon completion, this study will contribute knowledge about the potential risk for health effects associated with the higher ambient Mn air measured in East Liverpool.

East Liverpool has 13,089 residents and is similar in size to the two towns (Marietta: 14,515 residents and Mt. Vernon: 14,375 residents) currently being studied by the investigators (see Appendix C). East Liverpool is also similar to these two towns in ethnic and gender

proportions, median age, and income; however, the percentage of residents living below poverty in East Liverpool is higher than in Marietta and Mt. Vernon. The percent of residents having less than a high school education in East Liverpool (26.6%) is higher than in Marietta (15.9%) and Mt. Vernon (19.8%) and fewer residents of East Liverpool are college graduates or have post-graduate degrees. Both Mn-exposed towns, Marietta and East Liverpool, are situated on the Ohio River and both have Mn polluting industries near the city. Both Marietta and East Liverpool have industrial plants with documented chemical emissions, with Mn being the pollutant of greatest concern. The exposed town of Marietta has an industrial complex with a ferroalloys facility, Eramet, being the main point source for Mn emissions. Modeled Mn air emissions in Marietta have been shown to range from 0.04 to 0.96 $\mu\text{g}/\text{m}^3$; while East Liverpool, the proposed more highly exposed town, has Mn-air concentrations ranging from 0.10-23.0 $\mu\text{g}/\text{m}^3$. Mn exposure for Mt. Vernon was considered to be low based on data from the Toxic Release Inventory, and the town was therefore selected as a comparison/control town.

Study Design: The proposed health study will utilize a cross-sectional design using a Mn-exposed group of 100 residents of East Liverpool drawn at random as an add-on to the 100 exposed residents from Marietta and 90 comparison residents from Mt. Vernon, who are part of a prior study currently being completed. As for the prior study, the same age group (30-75 years of age), and the same methods of selection/recruitment, inclusion and exclusion criteria, and neurological and neuropsychological test measures and procedures will be used in this current study of East Liverpool, Ohio. The prior study conducted in Marietta and Mt. Vernon, had received IRB approval from both SFSU and the Ohio Department of Health (ODH).

- **Data collection methods:** The same carefully controlled and standardized test administration instructions as those used in the Marietta/Mt Vernon study will be applied to the data collection procedures in East Liverpool. To the extent possible, the testers will be the same as in the prior study. The test battery and test description are listed in Appendix B. All non-copyrighted questionnaires are also submitted to the IRB for approval. Additionally, an IRB protocol will be submitted to the US EPA, who have contracted the University of North Carolina to conduct their IRB reviews.

The data collected in this study will include the following:

1. Air exposure of Mn, already collected by the EPA/ATSDR for the period between 1999 and 2009 (9 years and 8 months).
2. Neuropsychological (including mood and motor efficiency) tests (see Appendix B of the enclosed proposal).
3. Neurological function will be assessed with the Unified Parkinson's Disease Rating Scale (UPDRS) administered by the same trained physician (2 subscales: Activities of Daily Living and Motor Function)
4. The CATSYS (Danish Product Development) – consisting of 4 postural sway conditions and hand tremor.

5. A health questionnaire containing sections on residency, symptoms, medical history, medications, work history and behaviors, diet, and personal demographic information (enclosed).
6. The possibility of worry impacting symptom reporting in the East Liverpool group will be addressed in two ways: A) we will include an Environmental Worry Scale (EWS, enclosed), scores of which will be analyzed as a potential confounder and B) all examiners will be (most already are) trained in detecting symptom and cognitive impairment exaggeration. Additionally, a short test of effort (Rey-15) will be administered, which if failed, will result in the administration of a highly regarded test of symptom validity, the Victoria Symptom Validity Test (VSVT). This test is designed to provide evidence that can confirm or disconfirm the validity of an examinee's cognitive and symptom impairments. In the event that the examinee fails both the Rey 15 and the VSVT, that participant's test scores will be excluded from the group analysis.
7. Whole blood will be analyzed for levels of manganese (Mn), mercury (Hg), cadmium (Cd), and lead (Pb) and serum will be used to evaluate ferritin and the liver enzymes, alanine-aminotransferase (ALT) and gamma-glutamyltransaminase (GGT). Toenail and hair samples will be analyzed for levels of Mn. In total, 12 mL whole blood will be collected from each participant for analyses. Whole blood samples will be shipped on dry ice by Fed Ex immediately to the CDC and serum samples to the U.S. EPA NHEERL Core laboratories. The samples will be identified by each participant's ID number only and no names will be included

The ATSDR, represented by Dr. Michelle Colledge, will be collaborators on the proposed project to assist on the analysis of the monitoring data from the East Liverpool region. Dr. Danelle Lobdell, an epidemiologist from the U.S. EPA National Health and Environmental Effects Research Laboratory, Human Studies Division, will serve as the Technical Consultant on the project. The data of Mn in air collected over the 9 years and 8 months and published in the November 2010 Health Consultation report, will be the basis for determining external Mn exposure. Additionally, internal Mn dose will be assessed through the analyses of Mn in blood, hair, and toenail analyses for the presence of Mn in the body. The study of the East Liverpool group will enable the comparison of the residents' neuropsychological test performance, motor efficiency, movement, and function on postural sway and hand tremor with that of the Marietta and Mt. Vernon groups and with established normative data. The information collected from the medical, social, and psychological history questionnaire will be used to control for factors (other than exposure to Mn) that could affect an individual's test performance. The use of standardized and well-recognized tests will also allow us to examine the neuropsychological test performance data in relation to the exposure data (both internal and external) to determine the presence of dose-dependent differences in neuropsychological function.

- **NEUROPSYCHOLOGICAL TESTS AND DESCRIPTIONS**

The test battery and test descriptions are listed in Appendix B.

- **Data Analysis Plan**

In order to compare scores on neuropsychological, motor and mood tests, and the UPDRS between the three towns, the general linear model will be used. This will test for differences between participants in the three towns, including pairwise comparisons for differences in domains of neurological, neuropsychological, mood and motor functioning, with covariates included in the model as necessary. Logistic regressions will be used for dichotomous outcomes such as symptom and illness frequencies in each town, comparing the relative risk between the samples after controlling for the effects of covariates.

Multiple regression analyses will test for relationships between Mn levels in air, blood, hair, and toenails, and neuropsychological test scores in East Liverpool, and these relationships will be compared to the results recently obtained in Marietta. Logistic regressions will be used for categorical outcomes to examine the relationship between Mn levels in air and risk for particular illnesses or symptoms and mood.

Power analyses using G*Power statistical software indicated adequate statistical sensitivity with a sample size of 100. Setting power at 0.80 and alpha at 0.05, one-way between groups analyses of means would be powered to detect an effect size of $f=0.18$ or greater. This is halfway between a small and medium effect size based on Cohen's (1988) guidelines, and should be sufficiently sensitive to detect the effects of manganese exposure in this sample, based on theory and previous research.

- **Limitations of the available Exposure Estimates**

The current proposal does not include individual quantitative estimates of actual air Mn exposures but the monthly averages of Mn in air monitored in the area studied will be used to model exposure. Questionnaires and biomarker results will be used to help rule out confounding exposure from other chemicals analyzed in blood and from effect modifiers measured in serum. The understanding is that the current proposal's "exposure assessment" includes only one group of East Liverpool participants residing within 2.5 miles of the Water Plant air monitor who have on average about 10 x greater airborne Mn exposure than residents in Marietta. The basis for this exposure assumption is described above. Dietary information of foods containing Mn, Mn in diet supplements, and Mn in blood, hair, and toenails will be collected and analyzed with the functional variables assessing possible dose-effects. This study is supplemental to the pilot study for the larger proposed ATSDR study and has a narrow focus on neurobehavioral and health outcomes in relation to Mn in ambient air, blood, hair, and toenails, with diet as an additional surrogate for Mn.

- **Significance:**

1. This study will contribute to the knowledge of effects of environmental exposure at different levels to airborne Mn on neurological and neuropsychological functions of randomly selected adults.
2. Although Mn exposure has been reported in numerous studies of occupational workers, very few reports of environmental Mn exposure are available. This study will add to the findings of the Marietta study by investigating a much higher exposed town, which will contribute to

- knowledge about environmental Mn data in air and in blood, hair, and toenails, and the level of exposure that may be related to developing symptoms associated with Mn exposure
- knowledge of the relationship of Mn in air to neurological, neuropsychological, and health status
- addressing concerns about potential health effects in the exposed town of East Liverpool when comparing the adult test data to that of Marietta and Mt. Vernon and to normative ranges of unexposed populations
- piloting and refining the study methodology for a larger study being planned by the ATSDR

2. PARTICIPANT POPULATION

a. Participants: The proposed health study will recruit 110 individuals (10 will be alternates if there are cancellations) residing within 2.5 miles of the Water Plant air monitor in East Liverpool, Ohio. Due to the demographic similarities between East Liverpool and the two communities already studied, the selected participants are expected to be similar on age, gender, ethnicity, and level of education (Appendix C).

b. Inclusion criteria

To be included in the study, participants must be 30-75 years old and have 10 years or more of residency in East Liverpool. Participants must live in homes serviced by the municipal water supply and must reside within 2.5 miles of the Water Plant air monitor in East Liverpool, Ohio.

c. Exclusion criteria

1. having had a major occupational exposure to pesticides, fungicides, or herbicides, carbon monoxide (CO), or other heavy metals requiring a medical visit,
2. a diagnosis of a psychiatric, neurological, or hepatic medical condition, including: stroke, electroconvulsive treatment, epilepsy, brain surgery, encephalitis, meningitis, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's dementia, schizophrenia, bipolar disorder,
3. current treatment for alcohol or drug dependence,
4. prior head injury or a stroke resulting in hospitalization for more than 1 day,
5. having worked at S.H. Bell or Eramet Marietta Inc. at any time,
6. women who are pregnant or nursing.

RECRUITMENT

Participant recruitment will be preceded by public announcements of the study. The recruitment plan is outlined below.

a) Community Meetings and Health Study Announcements

1. Community meeting announcements will be made via radio, newspaper, and television.
2. The study P.I. and her assistant will travel to East Liverpool on September 14th, 2011 to meet with the Health Commissioner and her board, on September 15, 2011, presenting the study. The same evening, a meeting for the community will be held to describe the study as outlined below in # 3 open to the residents and other interested parties of East Liverpool.
3. The community meeting in East Liverpool will consist of a presentation of a brief slide show, previously presented at the Marietta, Ohio community meeting but revised for East Liverpool. Around the time of the community meeting, invitation letters will be mailed to all residents within a 1 mile radius of the Water Tower monitor and to a random sample of approximately 1/3 East Liverpool households within the 1-2.5 mile area, selected at random from a purchased list of postal addresses. The letter will describe the East Liverpool Community Health Study and its procedures. The letters will also contain a stamped, self-addressed postcard where residents will be able to indicate their interest in study participation if they are eligible (determined by a phone call interview after the cards are received in the research office).

b) Recruitment Procedure:

1. The sample of households in the area of 2.5 miles surrounding the East Liverpool Water Plant air monitor and S.H. Bell will be obtained from the 911 database, and a purchased list of all complete postal addresses.
2. Letters will be mailed to all residents within the 1 mile area from the Water Plant air monitor and a randomly selected group of addresses representing 1/3 of the database containing the postal addresses for the 1-2.5 mile area. The letters will contain a self-addressed, stamped card which could be used to indicate willingness to participate or denial to participate in the health study. If participants indicated interest, a brief questionnaire listing the exclusion factors will be administered during subsequent telephone calls to the participants. If the number of return cards received 2 weeks after the mail out is insufficient, the research team will attempt to contact potential participants via telephone. In an attempt to reach potential participants, a maximum of three phone calls will be made to those who have an answering machine and a maximum of five phone calls for those who do not have an answering machine. The telephone numbers will be obtained from an East Liverpool telephone book or the white pages. If the responses are insufficient in number, this process will be repeated until 110 adults are available to be tested or until the maximum number of phone calls has been

reached for each potential participant (10 alternates are included to be called if any of the first 100 participants cannot come in the last few days prior to the appointment).

3. Calls will be made until 110 individuals agree to participate.
4. Selected participants will be contacted by telephone 4 weeks prior to the study to set up appointments at a convenient location.
5. Two days prior to the appointment, telephone appointment reminder calls will be made.
6. Because of concern and interest about chemical exposure, a relatively high response rate of ~50% is expected in East Liverpool.

STUDY PROCEDURES

1. The above recruitment methods will be followed.
2. Examiners will meet the day prior to testing and set up testing areas, review all test administrations and set up stations and offices where consent forms, interviews, and tests will be administered.
3. At the time the study will begin, scheduled study participants in groups (three groups per day) of 11 people (+ 1 extra person on one of the days) will be seated in a common area and greeted by the P.I. who will give a brief introduction about the study, the procedures, and the consent form.
4. The P.I. will interview all of the participants with a brief, somewhat structured interview schedule, asking participants about special concerns, fears and observations related to their exposure. The check-out staff person will at this time collect and de-identify the participant's list of current medications, (copied each night at the conclusions of testing) which will be hand-carried in carry-on luggage by the P.I.
5. Trained examiners will introduce themselves to participants and will explain the consent form in detail. Participants will be given time to ask questions. Then two copies of the informed consent will be signed; one for the participant and one for the researcher.
6. The participant will be invited to accompany one of the testers to a private room for testing. The neuropsychological testing will be conducted without any identifiers on the test protocols other than the respective I.D. number. Examiners will be two neuropsychologists and six graduate students in psychology, who will be trained by the P.I. and senior staff (all have completed the course for the protection of human subjects – certificates enclosed).
7. After completion of the tests, the study staff will introduce participants to the certified phlebotomist, who will draw a total of 12 mL of venous blood from each participant for analysis. The Centers for Disease Control and Prevention (CDC) Environmental Health Laboratory has agreed to perform the blood analyses of whole blood for Mn, Pb, Cd, and Hg levels. Ferritin levels, and ALT and GGT activities in serum will be determined by the U.S. EPA NHEERL Core laboratories. A total of 200 samples (two vials per participant, 6 mL each) of whole blood will be collected from study participants by the licensed and trained phlebotomist/medical technician. Presumably, one needle stick per participant

(or as few as needed) will be used by the certified phlebotomist/medical technician. Four mL of whole blood will then be centrifuged at 800 x g for 10 min at room temperature to separate the serum. Whole blood will be kept at 4°C and serum samples will be immediately stored at -18°C until analysis and sent weekly by Express Mail to the laboratory. Half a milliliter of serum is needed for the analysis of ferritin concentrations by immunoturbidity using the Roche Tina-quant assay on the Hitachi 912 clinical analyzer. Also half a milliliter of serum is needed to analyse the activities of the liver enzymes ALT and GGT with a Beckman Synchron LX20 using an enzymic rate method. The usual QA/QC methods of the CDC Laboratory will be applied. Each analytic run is surrounded by at least two levels of bench quality control and one blind quality control sample is inserted with each run (40-60 samples). The methods are CLIA-certified and multiple PT are run, as available. The DLS QA/QC system (Caudill et al., 2008) is referred to as the Multi-Rule Quality Control System (MRQCS). The CDC rules are similar in nomenclature to Westgard's format, but the rules are not identical. Some of the additional features of MRQCS include the ability to distinguish between within-run and among-run precision, accommodating variable numbers of QC measurements per run and accommodating variable numbers of QC samples per pool. Quality control measures include analysis of initial calibration verification standard (National Institute of Standard and Technology standard reference material (NIST SRM) 1643e (trace elements in water, Gaithersburg, MD), a solution of NIST traceable 1 ng ml⁻¹ manganese standard as the continuous calibration verification standard, procedural blank and Certified Reference material GBW 07601 (human hair) (Institute of Geophysical and Geochemical Exploration, Langfang, China) will be used as the quality control sample. Results will be given as the average of five replicate measurements of the instrument. Recovery of the analysis of QC standard by this procedure is 90% -110% and, precision is given as %RSD (SD*100/Mean) and for hair samples it varied from 1%-25%.

8. Hair samples will be collected using the following procedures: The collector will first evaluate the presence of sufficient hair on head for collection. Approx. 1-3 cm of hair should be available for collection. The scissors will be cleaned with an alcohol swab in front of the participant. Hair will be cut as close to the skull as possible from the base of the skull near the point halfway between the spine & ear (lower right or left quadrant). When enough mass is an issue, typically on men, smaller snips of hair will be taken in a random pattern. The side of hair sample that was close to the scalp will be marked by tying that end off with sewing thread and the collected hair will be placed into a small plastic bag with the participant's id clearly indicated on the bag. All small bags will be sealed and placed into a container and sent to the laboratory for analysis.
9. Toenail samples will be collected in the following manner: A pair of titanium dioxide nail clippers will be rubbed with alcohol swabs to be thoroughly cleaned between people. Participants will be asked to clip their nails from all ten toes onto a clean paper (to make it easier to catch all the clippings) and place the collected nails in a small plastic bag labeled with their respective ID. All small bags will be placed into a container and send to the laboratory for analysis.

Whole sample (Hair/Toenails) will be pre-cleaned with 1% Triton X-100 solution prior to analysis to remove extraneous contaminants. Samples will be acid digested using ultra pure nitric acid at room temperature for 24 hours. Diluted samples will be analyzed for manganese using inductively coupled plasma mass spectrometry (ICP-MS, DRC-II, Perkin Elmer, Norwalk, CT) using indium as the internal standard.

- 10.** Two post-baccalaureate level students who were also part of the testing team in Marietta and Mt. Vernon, OH, will conduct check-in and check-out and review the questionnaires and individual participant folders to ascertain that all tests have been completed before the participant leaves. This protocol completeness review will be performed in order to detect unintentional omissions. Participants will at no time be pressured to answer any items they choose not to answer.
- 11.** Upon completion of the study, a gift card for \$50.00 for a local store will be presented to each participant as a token of appreciation for participation in the study.
- 12.** Feedback of the group's results will be given to the community and all interested parties either in person or in written form during late summer of 2012. If additional funding becomes available, the P.I. will also present group results of the study in a community meeting in East Liverpool.
- 13.** After the conclusion of the study, a brief feedback report will be prepared and mailed to each participant reporting the individual's test scores (by domain of function) and results of biomarker analyses. This report will also indicate whether the test results were:
 - a) within the normal range
 - b) of concern, needing a referral to the family physician for further assessment by specialists as indicated.
- 14.** All relevant professional parties and city officials will be contacted and given feedback of the group's findings.
- 15.** All inquiries by the media will be answered by the team of investigators including the P.I., Mr. Greg Stein from ODH and Dr. George Bollweg, representing the Regional U.S. EPA. Prior to any release of data, results and talking points will have been presented to the entire group of investigators, collaborators and advisory board for input and final wording.

Research details

- The proposed study will take place in rented facilities at locations convenient for participants in East Liverpool, Ohio (the Motor Lodge hotel). The P.I. has made sure that they offer the privacy needed for conducting the study procedures.
- Each participant will be engaged in the study procedures for an average of 2.5 to 4.0 hours.
- It is expected that the brief introduction to the study by the P.I. and consent procedure will take no longer than 10 minutes since participants will already have received detailed information in the recruitment letters. Participants will be engaged in filling out

questionnaires for approximately 50 minutes, following which they will have a brief interview by the P.I. for about 10 minutes. The administration of the neuropsychological test battery is expected to take approximately 90 minutes. The administration of the CATSYS is expected to take 10 minutes. The neurological examination (UPDRS) will last 15 minutes. Participants will then have refreshments for about 10 minutes before being introduced to the certified phlebotomist for the drawing of the blood and hair sample collection, followed by the collection of toenail clippings by participants, which will each take 10 minutes.

4. RESEARCH RISKS

- Drawing venous blood from the arm may cause minimal pain when the needle is inserted. There is also a slight risk of bruising and infection where the needle punctures the skin. In rare cases, some people may experience lightheadedness, nausea, or fainting. The certified phlebotomist is trained in recognizing and dealing with these types of reactions. All possible accommodations will be made should this occur. Cutting a small amount of hair will be done with a blunted scissors which will prevent any accidental injuries. Blood samples will also be marked with an ID number only to ensure those analyzing the blood/serum are blinded to the identity of the participant. Arrangements will be made with a local physician on call, who will be recruited by a local colleague practicing in East Liverpool. The pager number and location of this local physician will be obtained so he/she may be contacted and available to address any medical emergency that may arise. Although such emergencies are highly unlikely, a participant, if necessary can be brought to the nearest Emergency Room at the local hospital.
- There is a risk of experiencing slight fatigue during testing. Testers are trained to look for signs of fatigue and a break will promptly be offered. The participants will also be informed that they can take a break or discontinue testing at any point.
- Participation may involve potential loss of privacy. To minimize this, results will be stored in a password-protected computer database with no identifying information attached. Hard copy files of all of the data will be kept by the P.I. in a locked file cabinet for 5 years with documents containing ID numbers only. Any documents or computer files linking ID numbers to names will be kept in a separate, locked file cabinet (or computer database) only accessible by the P.I. and will also be destroyed after 5 years.

5. CONFIDENTIALITY

All test results will be linked to an ID number, with all personally identifying participant information removed. Results will be stored in an encrypted document on a password-protected computer and all paper materials will be stored in a locked file cabinet in Dr. Bowler's research office laboratory at 8371 Kent Drive, El Cerrito, CA 94530. Only Dr. Bowler will have access to information linking ID numbers and the identities of the participants. Each page in the participant's folder will be coded with an ID number only.

Security will be maintained by having an alarm system in the building and by having each staff member sign a special Data Contract to maintain confidentiality of the data, refraining from any public conversations about the participants. The data will not be released unless subpoenaed by a court of law. Anyone working on the data will also be required to sign this, guaranteeing confidentiality and guaranteeing that these data will not be used unless the P.I. is involved in order to guarantee privacy to the information given by the participant. All data will be maintained for approximately 5 years in hard copy, limiting access to only authorized individuals. The electronic data will be securely stored indefinitely. Unauthorized access will be reported to the relevant parties (IRB, participants, stakeholders). Electronic data will be saved on a device that has the appropriate security safeguards, such as unique identification of authorized users, password protection, automated operating system patch (bug fix) management, anti-virus controls, firewall configuration, and scheduled and automatic backups to protect against data loss.

6. BENEFITS

Participants will receive the test results in writing, which they can send to their physician. We will indicate whether any results are of concern. If abnormalities are found, they will be referred to your family physician.

7. PAYMENT

Upon completion of the study, a gift card for \$50.00 from a local store will be presented to each participant as a token of appreciation for participation in the study.

8. COSTS

There is no cost for taking part in the study, aside from the transportation costs of coming to the appointment. Transportation costs involved in coming to the facility, which will be selected to be convenient for participants, will not be reimbursed. The researchers, research team and sponsors of this project will not provide medical care nor cover the cost of medical care for participants.

9. ALTERNATIVES

The alternative is not to participate in the research.

10. CONSENT/ASSENT PROCESS AND DOCUMENTATION OF CONSENT

a. The study will first be introduced to East Liverpool residents at the community meeting that will take place in September 2011. A slide show detailing the study procedures for the community residents will be presented. Residents will be informed that they might receive a letter from the P.I. containing the study description. If selected, residents will be asked to complete and return a stamped, self-addressed card indicating willingness or non-willingness to participate to the P.I. Participants will be able to have their questions answered during the recruitment and screening calls, as well as later, at the time of the appointment. They will be able to ask the P.I. any additional questions that may arise either on site after the meeting or over the telephone when they are administered the inclusion/exclusion questionnaire. They

also will be provided additional time to ask questions when the IRB approved consent forms are explained and reviewed by the examiners with each participant at the time of testing. The consent forms will be kept in each participant's testing protocol folder for the duration of the study procedure. Upon arrival at the P.I.'s office, the consent forms will be removed from the folders containing the participants' test protocols and will be in possession of the P.I. , along with the list connecting IDs and names. These forms will be kept in a locked file cabinet in the P.I.'s office.

- b.** Participants will receive a signed copy of the consent form.

11. INVESTIGATORS' QUALIFICATIONS

All investigators and trained examiners/psychometricians hold valid NIH Ethics Certificates and will follow the usual confidentiality rules. They will not have names of the participants on their protocol they may score and review. The following are the team of experts conducting the study:

a. **Professor Rosemarie Bowler** is a licensed neuropsychologist, qualified medical evaluator, and an emerita lecturer at SFSU. She has published numerous research articles on neurotoxicants and their effects on health. She has previously been on the committee at the National Academy of Science, Institute of Medicine and has served on the CDC/ATSDR Board of Scientific Counselors. She has taught at SFSU since 1977, recently retired, but is still teaching, training and supervising SFSU Psychology graduate students, as well as Ph.D. students in other universities. Professor Bowler has conducted numerous studies of neurotoxicity in adults and has also been responsible for 5 major epidemiologic studies of the effect of neurotoxicants on children (in California, Ohio, France and New Mexico). She has served on numerous committees and boards regarding the chemical effects of exposures on human populations.

Dr. Danelle Lobdell, an epidemiologist from the USEPA at Chapel Hill, NC, is the technical advisor on the project. She will give input on aspects of exposure, selection, statistical analyses and general communications with the community, federal, state and local agencies, and community and scientific presentations. She will be a co-author on manuscripts.

Dr. Harry Roels, Université catholique de Louvain (UCL), Brussels, Belgium. Professor Roels has a long history of scientific work with human populations exposed to neurotoxicants. Professor Roels is one of the most well-known scientific experts on Mn, in fact his study of battery workers in Belgium resulted in the lowering of the Threshold Limit Values (TLVs) of Mn. Dr. Roels is a sought out international expert on Mn and is on many international federal committees on scientific issues related to Mn. He will work closely with the P.I. on all neurotoxicologic and epidemiologic areas of the study and be a co-author on all manuscripts.

Dr. Michelle Colledge, Environmental Health scientist, Division of Regional Operations for Region 5 of the US EPA and ATSDR, conducted the health consultation detailing Mn exposure in EL for almost 9 years. She authored the East Liverpool Air Quality Report, November 16, 2010.

Dr. Colledge will assist the P.I. and Dr. Roels on all aspects of selection of the area to be studied, air exposures, the design of analyses using the air data and the analyses of potential relationships between the neurological, neuropsychological and health data and Mn exposure. She will be a co-author on all papers.

Dr. Yangho Kim-Department of Occupational and Environmental Medicine, Ulsan University Hospital, College of Medicine, South Korea. Dr. Kim has previously conducted the neurological examinations using the UPDRS in the Marietta and Mt. Vernon studies and has submitted a manuscript on these findings. He will again administer the UPDRS to all participants in EL and likely will author manuscripts with the research team on the results of the neurological function in EL, comparing the results to normative data and to the data collected from his examinations of residents in Marietta, OH and Mt. Vernon, OH.

Dr. George Bollweg, US EPA Region 5, environmental health scientist, will assist the P.I. and study team on issues of exposure to Mn and other substances. He is a collaborator and will give input on all issues related to Mn exposure in air and biomarkers. He will be a co-author on manuscripts and facilitate communication with the public and the Region.

Mr. Greg Stein, (ODH), community involvement and health education co-ordinator, will assist the P.I. with community involvement and communications and media related activities. He will assist with the production of media materials and community friendly fact sheets announcing the study, giving results and feedback of the study and also will assist with the health effects results of the study and communication to participants and stake holders. He will be co-author on manuscripts describing the overall study, methods and results.

Trained examiners/psychometrists:

Vihra Gocheva, MA (pending, San Francisco State University)

Matthew Harris, MA, Ph.D. (pending, Alliant International University)

Linda Mora, Ph.D., Oakland Children's Hospital

Katherine Wilson, MA, Ph.D. (pending, Alliant International University)

Beth Stutzman, MA, Psy.D. (pending, The Wright Institute)

Matthew Beristianos, MA, Ph.D. (pending, Alliant International University)

Katherine Brown, Psy.D. (pending, Alliant International University)

CATSYS administrator - Ralph Rasalan, MA (pending, San Francisco State University)

2 trained psychology students-TBA

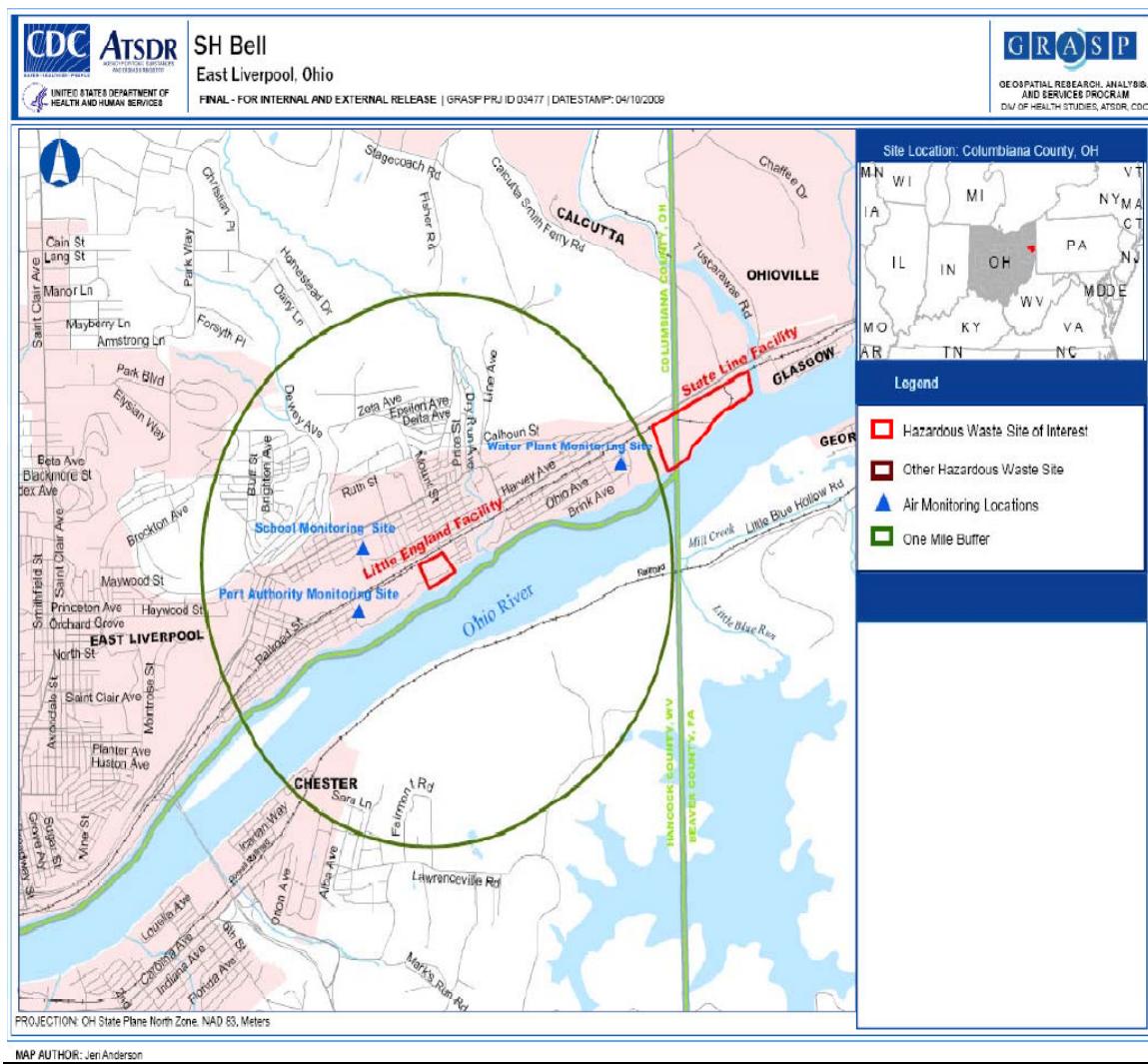
1-2 additional trained data-entry persons from psychology research classes at SFSU

12. FUNDING SOURCES

Funding by the USEPA is awarded as a contract from July 20, 2011 to July 19, 2012. The study will commence immediately once final approval is given, and testing will take place on November 3, 4, 5, and 6, 2011. The main contact person responsible for communication of the cooperative at the U.S. EPA is Dr. Edward Hudgens from the U.S. EPA. Dr. Danelle Lobdell is the technical advisor at the National Health and Environmental Effects Research Laboratory in

Chapel Hill, NC. The contact person for EPA at Region 5 is Dr. George Bollweg. Funds will be processed through the Office of Research and Sponsored Programs (ORSP) at SFSU. No conflict of interest exists for any of the researchers.

Appendix A. East Liverpool Area Map in Relation to the 3 Air Monitor Sites



Appendix B. East Liverpool Test Battery

I. NEUROPSYCHOLOGICAL BATTERY (120 MIN)

A. Cognitive (90 min):

1. Animal Naming
2. Digit Symbol Coding
3. Rey-O Copy
4. Digit Span
5. Rey-O Immediate
6. ACT
7. Stroop Color Word Test
8. Trails A & B
9. Similarities
10. Rey-O delayed
11. NAB Memory
12. REY-15
13. Victoria Symptom Validity (if needed, based on Rey-15 scores)

B. Motor & Tremor :

- CATSYS
- Grooved Pegboard
- Fingertapping
- Dynamometer
- Parallel lines

C. UPDRS – ADL and Motor (15 minutes)

D. Mood:

- SCL 90-R
- BRFSS
- Satisfaction with life Scale
- Environmental Worry Scale (EWS)

II. SELF-REPORT QUESTIONNAIRES

- Health Questionnaire

III. BIOMARKERS & AIR MEASUREMENTS

A. Blood:

- Mn, Pb, Hg, Cd

- B. Hair
 - Mn
- C. Toenails:
 - Mn -10 toenail clippings
- D. Serum:
 - Ferritin

Test Battery Details

Cognitive Tests (In alphabetical order)

***Animal Naming* (Lezak et al., 2004):**

A category fluency test, requiring the naming of as many animals as possible in 1 minute.

***Auditory Consonant Trigrams (ACT)* (Lezak et al., 2004):**

A test of divided attention and concentration in which participants are orally presented with 3 consonant letters and a specified number from which they are asked to count backwards by three for 3, 9, or 18 seconds, at which point counting is interrupted and they have to recall the 3 consonants.

***Neuropsychological Assessment Battery (NAB): Memory Module* (Stern and White, 2003):**

A test with high ecological validity consisting of an array of subtests assessing learning and memory. Subtests include: list learning, shape learning, story learning and daily living memory with immediate and delayed recognition trials and forced-choice recognition.

***Rey-Osterrieth Complex Figure Test* (Meyers and Meyers, 1995):**

Assesses planning, organizational skills and problem-solving strategies and perceptual, motor and memory functions. To assess visuospatial constructional ability and visuospatial memory participants are asked to copy a complex figure and then to reproduce it after a 3 and 30 minute delay. It has been shown sensitive in Parkinson's disease and frontal lobe damage.

***Stroop Color and Word Test* (Golden, 1978):**

Measures the ease with which a person can shift his/her perceptual set to conform to changing demands and suppress a habitual response in favor of an unusual one. The test involves word reading, color naming, and set shifting (reading color names printed in a different color ink) and is sensitive to dementia, depression, PD, schizophrenia, Huntington's disease, and head injury. Color-blind subjects are excluded.

***Trail Making Tests (TMT)* (Strauss et al., 2006):**

Tests of speed of attention, sequencing, mental flexibility, visual search and motor function. It requires connecting in order encircled numbers or letters, randomly arranged on a page. Part A requires the connection of numbers in order, and part B requires the sequencing of numbers and letters in alternating ascending order.

***Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) Subtests* (Wechsler, 1997):**

Digit Span (3 min) – a measure of attention and sustaining concentration

Digit Symbol (3 min) – a spatial measure involving learning and speed

Similarities (10 min) – higher level verbal abstraction and reasoning, will also be used as an estimate of premorbid function

Mood and Health Questionnaires

Environmental Worry Scale (EWS) (Bowler and Schwarzer, 1991)

This scale is a 17-item measure developed to predict intention to avoid chemicals and has satisfactory psychometric properties. A 5-item version was used in this study to examine participants' particular concerns about chemical exposures, which is also has satisfactory normative properties.

Health-Related Quality of Life Scale (BRFSS)(Centers for Disease Control and Prevention)

This scale is a brief 4-item scale developed by the Centers for Disease Control and Prevention to assess self-perceived recent health, recent mental health and activity limitations. Nationwide normative data is available.

Satisfaction with Life Scale (Diener et al., 1985)

This 5-item scale is a brief measure of life satisfaction. It asks participants to compare the current status of their life to their self-defined expectations of how they would like their lives to be. It has satisfactory psychometric properties.

Symptom Checklist-90-Revised (SCL-90-R) (Derogatis, 1992)

A 90-item standardized scale asking participants to rate how much of a problem certain symptoms had been in the prior week, using a five-point scale. Domains/scales are: Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, Psychoticism, and summary indices.

General Health questionnaire:

A health questionnaire will be administered in a printed format. It will include socio-demographic information, smoking and drinking habits, hobbies with exposure to neurotoxic substances (gardening using pesticides, solvents, painting, welding etc), a history of illnesses and familial illnesses (with emphasis on neurological disorders), accidents and current symptoms (sleep, respiratory, cardiovascular, musculo-skeletal, neurologic and neuropsychiatric).

Tests of Effort

Victoria Symptom Validity Test (VSVT) (Slick et al., 2005)

This computerized test is used to assess effort on memory tests and memory complaints exaggeration. The VSVT includes the presentation of 48 five-digit numbers and the forced-choice delayed identification of that number. Protocols where the number of correct items is above chance (50%) are considered valid. (15 minutes).

Rey's 15-Item Visual Memory Test (Strauss et al., 2006)

It consists of a card with 15 printed items (letters, numbers and shapes) arranged in 3 columns and 5 rows. The examinee is told there are 15 different (emphasized) items to remember which are to be reproduced immediately on a blank sheet of paper following a 10-second exposure to the stimulus card. Although it is presented as a difficult task, it is actually quite simple because there is redundancy among items that reduces the amount

of information to be remembered (i.e. three main ideas). It is used to test motivation and potential deficit exaggeration.

Neurological examination

The motor/movement components and activities of daily living of the Unified Parkinson's disease Rating Scale (UPDRS) will be administered. The UPDRS is the most widely used scale for evaluation of clinical impairment in motor function. It contains 27 items, including assessments of posture, gait, postural stability, bradykinesia, and general hand and leg movements and tremor. It has good reliability and validity, utilizing the standardized test methodology and videotaped reference guide developed by (Goetz et al., 2003). It includes the Activities of Daily Living section (UPDRS II) and has 13 items of speech and daily activities and tasks. All items are rated on a scale of 0 (normal) to 3 or 4, depending on the scale with clinical descriptor for each rating ranging from normal to severe.

Movement, Motor and Tremor (*In alphabetical order*)

Computerized Adaptive Testing System (Danish Product Development, 1996)

- 1) **CATSYS hand tremor** test. Hand tremor will be measured using the TREMOR 7.0 Test System. Vibrations within each hand are recorded with the TREMOR PEN. A two-axis micro-accelerometer is embedded within the tip of the 12 cm x 0.8 cm TREMOR PEN, which is connected to a PC data log system. The TREMOR PEN is sensitive to vibrations that occur in a plane perpendicular to the PEN axis. Vibrations will be analyzed using the Fourier Power Spectrum, which plots the normalized power distribution (the relative harmonic contents) of the vibration measurement period in a frequency domain. The Harmonic Index, highly sensitive to abnormal tremor patterns, relates the Fourier Power Spectrum to that of a single harmonic oscillation.
- 2) **CATSYS postural sway** test. This test of postural stability will be performed in three conditions (35 seconds in each condition) while the participant stands on a 50 cm platform balance plate with a) eyes open , b) eyes closed, and c) eyes closed standing on 2 cm foam. Postural stability is measured in Mean Sway (mean of force center position to all recorded center positions), Transversal Sway (sway movement from side to side), and Sagittal Sway (sway movement back and forth). A Sway Index (in relation to normative age-adjusted data) is computed for each condition.

Fingertapping Test (Lezak et al., 2004)

A measure of bilateral psychomotor speed; The participant is asked to tap a lever as quickly as possible. Scores are the mean of five 10-second trials for each hand.

Grip Strength (Dynamometer) (Lezak et al., 2004)

A test of grip strength with two trials administered bilaterally.

Grooved Pegboard Test(Lezak et al., 2004)

Tactile speed and visuomotor coordination; Pegs are inserted in the slots as quickly as possible; pegs have a ridge on one side, requiring a rotation to line them up with the slots. Completion time is recorded for each hand.

Parallel Lines - Graphomotor Tremor(Lezak et al., 2004)

Graphomotor tremor will be assessed by drawing lines as straight as possible within defined 3-inch and 1-inch high boundaries without lifting the pencil from the paper. Qualitative evaluation of tremor by a neuropsychologist with ratings of within normal limits, mild, moderate, or severe.

Appendix C. 2000 US Census Demographic Factors

		East Liverpool	%	Marietta	%	Mount Vernon	%
NO. TOTAL POPULATION		13,089		14,515	--	14,375	--
PLACE OF BIRTH	% US-BORN (UB)	--	99.1	--	98.8	--	98.4
	% OH-BORN (OF UB)	--	74.2	--	66.7	--	81.5
	% FOREIGN-BORN (FB)	--	0.5	--	1.2	--	1.6
	% NON-CITIZEN (OF FB)	--		--	43.2	--	40.7
POVERTY	% BELOW POVERTY	--	25.2	--	16.9	--	15.6
RACE	NO. WHITE	12,153	92.8	13,979	96.3	13,895	96.7
	NO. BLACK	630	4.8	157	1.1	166	1.2
	NO. OTHER	27	0.2	379	2.6	314	2.1
ETHNICITY	NO. HISPANIC	94	0.7	114	0.8	125	0.9
SEX	NO. MALE	6,070	46.4	6,757	46.6	6,656	46.3
	NO. FEMALE	7,019	53.6	7,758	53.4	7,719	53.7
AGE	MEDIAN AGE, YEARS	35.7		38.4	--	37.1	--
	MEDIAN AGE MALE			36.1	--	33.9	--
	MEDIAN AGE FEMALE			40.4	--	40.0	--
	NO. 65+ YEARS	2,100	16	2,573	17.7		18.3
	NO. FEMALE 15-45 YEARS (% ♀)			3,330	42.9	3,051	39.5
	NO. PRE-SCHOOL ≤ 5 YEARS			947	6.5	1,171	8.1
	NO. SCHOOL AGE 6-18 YEARS			2,400	16.5	2,429	16.9
	NO. 7-8 YEARS			351	--	406	--
	NO. 9-10 YEARS			325	--	370	--
	NO. 35-65 YEARS			5,412	--	5,075	--
	NO. 25+ YEARS			9,381	64.6	9,504	66.1
EDUCATION (FOR 25+ YRS)	% LESS THAN HIGH SCHOOL	--	26.6	--	15.9	--	19.8
	% HIGH SCHOOL	--	45	--	34.9	--	39.5
	% SOME COLLEGE	--	21.2	--	25.9	--	22.6
	% COLLEGE	--	2.7	--	12.8	--	10.9
	% MORE THAN COLLEGE	--		--	10.4	--	7.2
NO. HOUSING UNITS (HU)		5,728	--	6,609	--	6,713	--
	NO. URBAN			6,426	97.2	6,543	97.5
	NO. RURAL			183	2.8	170	2.5
	% BUILT BEFORE 1970			--	75.5	--	75.0
	MEDIAN YEAR BUILT			1948	--	1952	--
NO. HOUSEHOLDS (HH)				5,904	--	6,187	--
	AVERAGE HH SIZE, PERSONS	2.4	--	2.2	--	2.2	--
	MEDIAN HH INCOME	\$23,138	--	\$29,272	--	\$29,801	--

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